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Effect of treatment on oxidative and nitrosative stress markers in calves with septic arthritis

Vandana[1], Ankit Dahiya[2], K. Mahendran[3] and S. Dey[4†]

ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly-243 122 (Uttar Pradesh)

[1]PhD Scholar, [2]MVSc Scholar, [3]Senior Scientist and [4]Principal Scientist, Division of Veterinary Medicine, Indian Veterinary Research Institute, Bareilly

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The current study was conducted at calf section of Cattle and buffalo Farm under the LPM Division of IVRI with the main objective to understand the oxidant-antioxidant imbalances along with changes in HR, RR, temperature, TLC, TP, LDH and their mitigation using ascorbic acid as an adjunct in calves affected with septic arthritis presented with the history of inappetence, fever, pain and local swelling at the joint. Overall incidence was reported to be 2.94%, which was highest in Vrindavani calves. To determine the oxidant-antioxidant imbalance, glutathione and lipid peroxides levels were measured, which were found to be elevated in diseased animals indicating the oxidative cell injury in arthritis. Treatment regimen adopted including administration of antibiotic and anti-inflammatory drugs, antiseptic dressing along with ascorbic acid (an antioxidant) brought earlier improvement showing that correction of oxidative stress during the course of therapy is essential for faster clinical recovery. Effect of therapy was also reflected in the composition of synovial fluid in calves receiving antioxidant as an adjunct therapy.

***Key words**: Arthritis, Ascorbic acid, Calves, Oxidative and nitrosative stress, Sepsis*

Sepsis is a highly heterogenous syndrome that is defined as a combination of focal or generalized infection and dysregulated systemic inflammatory response (SIRS) to the presence of bacteria in bloodstream (Radostits *et al.,* 2007). Multiple bacteria can cause septicemia in adult cattle and in neonatal calves. Septic arthritis or joint ill is quite common in calves, especially within 1st eight weeks of their life. It is responsible for considerable morbidity and mortality in calves and economic losses (Wichtel *et al.,* 2003; Desrochers, 2004). Septic arthritis may be caused by direct trauma to the joint which can cause invasion of bacteria (primary infection), the extension of a periarticular infection (secondary infection) or haematogenous dissemination (tertiary infection) (Hardy, 2006). Most common being the haematogenous route. Failure of passive transfer of antibodies via colostrum predisposes the calves towards development of septic arthritis. After colonization of the synovium, there is release of a variety of enzymes, free radicals and other inflammatory mediators, which initiate a marked synovial inflammatory response (Meijer *et al.,* 2000). The disease is diagnosed based on the clinical signs, ultrasonography, radiography and bacterial cultures (Francoz *et al.,* 2005; Gagea *et al.,* 2006; Heppelmann *et al.,* 2009; Thrall, 2013). Inflamed and painful distended joints, heat, redness, pyrexia, lameness and anorexia are among the clinical signs reported in septic arthritis (Haerdi-Landerer *et al.,* 2010). The cornerstone of diagnosis of septic arthritis is the arthrocentesis (Tulamo *et al.,* 1989). Treatment of the septic arthritis is challenging due to the high costs involved, long duration of the treatment and only few antimicrobials can cross into the joint and maintain therapeutic concentration.

The aim of this study was to evaluate the oxidative and nitrosative stress markers and effect of ascorbic acid as an adjunct along with principal therapy on these markers in calves affected with septic arthritis.

Materials and Methods

The study was conducted in calf section (Cattle & Buffalo) of Livestock Production and Management (LPM) Division of the institute from March 2023 to August 2023. The samples were collected from bovine calves of different breeds under the age of 6 months reared at calf section of LPM to study the incidence and to evaluate the different therapeutic interventions for septic arthritis management. Those calves which were suspected for joint disorders were subsequently screened for presence of two or more of the joint disorder criteria (joint mobility, pain, swelling, lameness, myositis, abscess and drainage) and all these suspected calves were also screened for sepsis based on the presence of at least two of the SIRS (systemic inflammatory response syndrome) criteria like temperature (>103.1°F or <98.6° F), heart rate (>160, <100 beats per min) and respiration rate (>45 breaths/min), WBC >12000 cells/µL or <4000 cells/µL) (Yildiz *et al.,* 2018; Beydilli and Gökçe, 2019). The animals having grade 2 at least for four of these above-mentioned joint disorder criteria were selected for the study categorizing each parameter into a clinical score of 0-3 (0 being normal, 1 for mild, 2 for moderate and 3 severe) along with fulfilling the SIRS criteria.

†Corresponding author; E-mail: sahadeb.csmlab@gmail.com

Severely affected animals were excluded from the study.

Based on this, 9 calves were found to be suffering with septic arthritis and one severely affected animal was excluded from the study. They were randomly divided into 2 groups of 4 animals each. Group 1 was provided with the antibiotic (Intacef –tazo, 20 mg/kg body wt, i.v.), cox-2 inhibitor (Meloxicam, 0.2 mg/kg body wt, i.m.), ascorbic acid (50 mg/kg body wt, s.c.) and antiseptic dressing (povidone iodine). The calves in group 2 were also provided with the same treatment except ascorbic acid. To compare between treatment groups, healthy calves devoid of any ailment were taken as control.

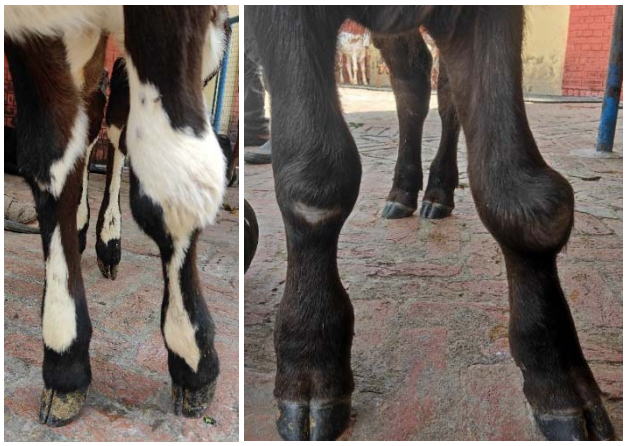

Fig. 1: (a) Swollen carpal joint in a cow calf; (b) Swollen carpal joint in Murrah calf

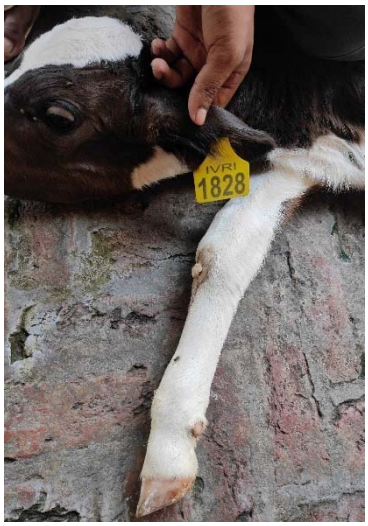

Fig. 2: Swollen carpal joint with exudation of pus

Blood (10 mL) was collected on day 0, 7 and 14, post-therapy in EDTA vials following aseptic measures using 18G needle from the jugular vein for haematology. Serum was collected after centrifuging the samples at 3000 rpm for 20 min, preserved at -20p C until further analysis. Serum samples were processed for different biochemical parameters such as total protein following manufacturer's protocol (Tulip Diagnostics Pvt. Ltd, Goa, India), serum lactate dehydrogenase (SLD) activity by optimized DGKC, Kinetic assay method (Pesce, 1984).

Haemolysate (10%) was prepared from packed erythrocytes by lysing it with triple-distilled water in a ratio of 1:9. To determine haemoglobin in this 10% haemolysate (mg/mL), cyanomethaemoglobin technique was used (Van Kampen and Zijlstra, 1961) to express lipid peroxide level (determined following the method of Placer *et al.,* 1966) and glutathione activities in erythrocytes by 5, 5′ dithiobis (2-nitrobenzoic acid) (DNTB) method of Prins and Loos (1969). Nitric oxide was estimated according to Sastry *et al.* (2002) procedure which was based on reduction (nitrate to nitrite) principle by Cu-Cd alloy. That was followed by quantification (colour development) with sulfanilamide and N-naphthylethylene diamine in acidic medium (Griess reagent).

Arthrocentesis was done after taking permission from Institutional Animal Ethics Committee (IAEC) for collection of synovial fluid from affected joints after hair clipping and locally disinfecting the joint. A 20 G (5 cm long) hypodermic needle was then inserted deep into the joint, till a drop of synovial fluid was seen at the hub of needle. Once the needle was fixed in desired position, a sterilized 10 mL glass syringe was mounted and synovial fluid was withdrawn for determination of TLC, DLC, pH and total synovial protein.

Immediately after collection, colour, turbidity and pH of synovial fluid were recorded. Total leukocyte count and differential leukocyte counts were done as per standard procedures described by Jain (1986) and Coles (1980), respectively. Total synovial protein was estimated in supernatant obtained after centrifugation of synovial samples at 3000 rpm for 15 min as per the method described for serum.

The data were analyzed using the commercially available software Statistical Package for the Social Sciences (SPSS) version 26.0 for windows and were expressed as mean±SE where $P<0.05$ values were considered significant. The post-hoc Tukey test was used to compare the group means when an ANOVA revealed a significant treatment effect.

Results and Discussion

During the study period, the overall incidence of septic arthritis recorded in calves was 2.94%, among a total of 306 calves belonging to Vrindavani (137), Tharparkar (52), Sahiwal (31) cattle and Murrah buffaloes (86). Similar prevalence (5-15%) of septic arthritis was also reported earlier in newborn calves (Rao *et al.,* 2020, Pas *et al.,* 2023). The incidence of septic arthritis in Vrindavani, Tharparkar and Murrah buffalo calves was 4.38% (6/137), 1.92% (1/52) and 2.33% (2/86), respectively. This indicates that the occurrence of septic arthritis was highest in Vrindavani cross-bred calves as compared to indigenous Tharparkar and Murrah calves. That

might be due to hardy nature and more resistance of the indigenous animals against diseases.

Along with arthritic symptoms, 2/9 (22.2%) calves showed concurrent diarrhea, 6/9 (66.7%) calves had an umbilical infection and none of the calves showed respiratory disorders. Haematogenous route was suspected to be the prime origin of the septic arthritis in most of the calves, except in one case of trauma.

All cases were presented with the history of presence of inappetence, fever, local swelling at the joint, fatigue, hot and painful joints. Similar findings were reported by various authors like Desrochers (2004), Desrochers and Francoz (2014), and Dogan *et al.* (2016). Medical treatment was given for 2 weeks in these animals and clinical improvement was seen in all cases except in 1 case which was later excluded from the study. Joint swelling gradually decreased in these animals and they started consuming feed by about 4th day of the treatment. Failure of treatment in one case may be due to chronic nature of the disease and consequently the fibrosis of the joint. Weaver (1997) and Orsini (2002) had reported the distension of affected joints in acute cases due to synovial effusion and peri-articular oedema, and thickening and fibrosis of the joint capsule in chronic cases (Butt, 2002).

A significant (P<0.05) increase in rectal temperature (RT) and respiratory rate (RR) (Table 2) was recorded in arthritic animals on day 0. No significant differences in RT and RR were observed between treatment groups on days 7 and 14; however, all groups showed linear decrease in values within the normal physiological range. Heart rate (HR) was non-significantly higher in group 1 and 2 as compared to healthy calves and it decreased on subsequent days of therapy in both treatment groups. The increase in these clinical parameters may be attributed to inflammatory nature of the disease caused by intra-articular infection by various pathogens. These results are similar to the findings of Ercan *et al.* (2016). Gradual returning to normal physiological values showed the effectiveness of the treatment in both groups. Mean serum total protein values were within

Table 1: Clinical and physiological parameters (Mean±SE) in animals of different groups at various intervals.

Sl. No.	Parameter	Day	Group 0 (Control) (n=5)	Group 1 (n=4)	Group 2 (n=4)
1	Rectal Temperature (p F)	0	102.31 ± 0.25^{bA}	103.73 ± 0.46^{aA}	104.00 ± 0.24^{aA}
		7	101.69 ± 0.32^{aA}	101.93 ± 0.80^{aA}	102.23 ± 0.27^{aB}
		14	101.40 ± 0.31^{aA}	101.50 ± 0.37^{aA}	101.58 ± 0.51^{aB}
2	Heart Rate (beats/min)	0	123.00 ± 4.25^{aA}	142.50 ± 20.88^{aA}	141.25 ± 22.60^{aA}
		7	130.00 ± 4.93^{aA}	124.25 ± 5.20^{aA}	121.75 ± 3.68^{aA}
		14	130.60 ± 2.89^{aA}	123.50 ± 6.54^{aA}	133.25 ± 3.64^{aA}
3	Respiratory rate (breaths/min)	0	23.60 ± 1.21^{bA}	31.25 ± 1.31^{aA}	32.50 ± 1.32^{aA}
		7	24.00 ± 1.00^{aA}	24.75 ± 1.31^{aB}	24.25 ± 1.38^{aB}
		14	23.00 ± 1.00^{aA}	23.75 ± 1.65^{aB}	24.00 ± 1.47^{aB}
4	Total protein (g/dL)	0	6.38 ± 0.51^{aA}	6.26 ± 0.41^{aA}	6.99 ± 0.31^{aA}
		7	6.72 ± 0.29^{aA}	6.78 ± 0.29^{aA}	6.56 ± 0.42^{aA}
		14	6.85 ± 0.12^{aA}	6.45 ± 0.22^{aA}	6.41 ± 0.30^{aA}
5	Nitric Oxide (µmol/L)	0	3.01 ± 0.51^{bA}	4.90 ± 0.16^{aA}	5.05 ± 0.36^{aA}
		7	3.14 ± 0.46^{aA}	3.49 ± 0.65^{aAB}	3.98 ± 0.29^{aAB}
		14	3.00 ± 0.40^{aA}	3.15 ± 0.47^{aB}	3.50 ± 0.49^{aB}
6	TLC (*10^3/µL)	0	10.86 ± 0.56^{bA}	15.15 ± 0.80^{aA}	15.24 ± 1.37^{aA}
		7	9.48 ± 0.58^{bA}	12.61 ± 0.67^{aB}	12.81 ± 0.74^{aA}
		14	9.40 ± 0.59^{bA}	10.69 ± 0.35^{bB}	12.77 ± 0.37^{aA}
7	Lactate Dehydrogenase (U/L)	0	562.25 ± 33.02^{cA}	834.33 ± 29.01^{bA}	1024.71 ± 54.03^{aA}
		7	575.18 ± 18.08^{bA}	638.76 ± 43.68^{bB}	824.43 ± 51.03^{aAB}
		14	591.10 ± 16.54^{aA}	593.57 ± 51.97^{aB}	630.06 ± 47.63^{aB}
8	Glutathione (nmol/mL)	0	0.27 ± 0.12^{aA}	0.18 ± 0.08^{aA}	0.14 ± 0.05^{aA}
		7	0.25 ± 0.04^{aA}	0.18 ± 0.06^{aA}	0.18 ± 0.01^{aA}
		14	0.25 ± 0.06^{aA}	0.25 ± 0.09^{aA}	0.21 ± 0.01^{aA}
9	Lipid peroxidase (U/L)	0	19.06 ± 0.62^{cA}	32.05 ± 1.43^{aA}	25.47 ± 1.31^{bA}
		7	21.71 ± 0.72^{bA}	26.12 ± 1.32^{aB}	24.77 ± 0.71^{abA}
		14	18.76 ± 1.06^{bA}	23.29 ± 0.40^{aB}	22.55 ± 0.77^{aA}

Values with different alphabet superscripts (^{abc}) differ significantly (P<0.05) between different groups on same day; values with different alphabet superscripts ^{ABC} differ significantly (P<0.05) within the same group on different days.

the normal physiological range throughout the treatment period in all groups (Table 1).

TLC values (Table 1) were significantly (P<0.05) higher in the groups with the joint infection than the healthy control group on day 0. Hardy (2006) also reported neutrophilic leukocytosis and hyperfibrinogenemia in septic arthritis cases. TLC level improved on 14th day post-treatment; however, the effect was more pronounced in group 1 in which ascorbic acid was also given along with antibiotic and anti-inflammatory drugs.

A significant (P<0.05) elevation in lactate dehydrogenase values (Table 1) was recorded in the affected calves in comparison to healthy calves. A significant (P<0.05) reduction in its values was recorded on day 7 in group 1 as compared to group 2, suggesting higher efficacy of the treatment regimen in group 1 as compared to group 2. Srivastava *et al.* (2018) also reported elevation in LDH level in arthritis cases. Higher levels of cytokines in the joint tissue and plasma are responsible for the disruption of leucocytes. Disrupted leucocytes are accountable for the higher activity of LDH enzyme. The process involving pathological-induced tissue damage is responsible for increase in the activity of lactate dehydrogenase, which is cytoplasmic cellular enzyme (Thompson *et al.*, 1987; Wang *et al.*, 2013).

Nitric oxide (NO) is a short-lived signaling molecule that plays an important role in a variety of physiologic functions, including the regulation of blood vessel tone, inflammation, mitochondrial functions and apoptosis (Beltran *et al.*, 2000). Several studies in patients with rheumatoid arthritis (RA) have documented evidence for increased endogenous NO synthesis, suggesting that overproduction of NO may be important in the pathogenesis of RA. The inflammed joint in RA is the predominant source of NO (Pham *et al.*, 2003). In this study also, nitric oxide levels (Table 1) significantly (P<0.05) elevated in groups having arthritic calves as compared to healthy calves on day 0. After treatment, serum nitric oxide concentration in the different groups returned towards normal indicating that the treatment used helped reduce inflammation and changes in inflammatory mediators.

In the current study, the glutathione level in arthritis affected calves was non significantly lesser than healthy calves on day 0 (Table 1). Decreased glutathione levels were also reported by Cheng *et al.* (2022) in arthritis cases. Some studies also indicated the unaltered level of glutathione (Cimen *et al.*, 2000). This decreased glutathione activity level during detoxification process might indicate a degradation of antioxidant enzymes such as catalase, glutathione peroxidase etc. by free radicals. There was non-significant increase in the glutathione level in both treatment groups on 7th and 14th day post therapy and the values were comaparable to control group.

A significant (P<0.05) elevation in lipid peroxide values (Table 1) was recorded in erythrocytes of arthritic calves in comparison to healthy calves, indicating that joints were vulnerable to peroxidation due to oxidative cell injury in arthritis. This finding on oxidative stress in septic arthritis is in agreement with the earlier studies where higher LPO levels have been reported in rheumatoid arthritis (El-barbary *et al.*, 2011; Zhang *et al.*, 2023). The treatment regimen adopted in the present study in group 1 brought earlier improvement, probably attributed to ascorbic acid having antioxidant property. Correction of oxidative stress during the course of therapy was probably responsible for an early clinical recovery in these calves.

Arthrocentesis and subsequent cytologic and bacteriologic analyses of the synovial fluid are the complementary tests for the diagnosis and the management of septic arthritis. Synovial fluid collected from healthy calves was clear with almost watery appearance and transparent. It was slightly turbid, yellow to red coloured and viscous in diseased joints. Turbidity and dark colour appearance of synovial fluid could be due to inflammatory fluids, cartilage degradation and presence of infectious agents.

A significantly (P<0.05) higher values of total leukocytes and neutrophils (Table 2) were recorded

Table 2: Cytological and biochemical changes in synovial fluid of healthy and calves with septic arthritis receiving different treatment (Mean±SE).

Parameter	Day post-therapy					
	Group 0		Group 1		Group 2	
	0	14	0	14	0	14
TLC (*10^3)	0.25±0.04^b	0.26±0.08^a	22.11±0.93^a	0.22±0.11^a	20.73± 1.11^a	0.41±0.01^a
Neutrophils (%)	6.98±0.61^b	6.38± 0.39^b	77.05±1.74^a	7.08±0.55^b	75.92±2.13^a	12.45±1.17^a
Lymphocytes (%)	51.62±1.38^a	52.39±1.26^a	12.79 ±0.68^b	50.88±1.12^a	13.27±0.84^b	48.03±1.69^a
Monocytes (%)	37.7±1.36^a	36.7±1.68^a	6.17±1.00^b	38.43±2.46^a	8.5±0.61^b	35.7±1.78^a
Other cells (%)	3.7±0.51^a	3.6±0.57^a	3.88±0.43^a	3.63±0.56^a	3.75±0.32^a	3.82±0.55^a
pH	7.59±0.38^a	7.40±0.32^a	7.22 ±0.54^a	7.51± 0.48^a	7.49 ±0.66^a	7.33±0.57^a
Total protein (g/dL)	2.55±0.22^a	2.41±0.17^a	3.09 ±0.40^a	2.68± 0.34^a	3.12 ±0.32^a	2.77±0.36^a

Values with different superscript alphabets (^{abc}) differ significantly (P<0.05) between different groups on same day

on day 0 in arthritis groups indicating cellular infiltration. Neutrophil counts were reduced in both these groups on day 14 when compared to healthy control calves. Degree of reduction in neutrophil counts was more pronounced in group 1 than group 2 on 14th day post-therapy. Neutrophil infiltration indicated acute inflammation and subsequent reduction with treatment revealed the efficacy of treatment. All the animals received antibiotics to control the infection that further helped to bring the cellular changes and composition of synovial fluids to normal level, which supported the clinical observation of clinical improvement (reduction of swelling of joints) noticed 7 days after treatment.

Significant ($P<0.05$) increase in total lymphocyte as well as monocyte counts (Table 2) were recorded in both treatment groups on 14th day post-therapy. Alkaline pH was recorded in all the groups with a non-significant variation among different groups. Total protein was non-significantly higher in arthritis groups on day 0. On 14th day post-therapy synovial total protein concentration was almost comparable to values recorded in control calves indicating potent anti-inflammatory effect of the treatment.

From the current study, it was concluded that the occurrence of septic arthritis was highest in Vrindavani cross-bred calves followed by Tharparkar and Murrah buffalo calves. Most of the calves affected with septic arthritis were having concurrent infection such as naval ill or diarrhoea. There was imbalance in oxidant/antioxidant and nitrosative status in affected calves and recovery was hastened in calves in which ascorbic acid was used as an adjunct along with the principal therapy consisting of antibiotic, cox-2 inhibitor and antiseptic dressing.

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